Triceps Surae Hyper-Resistance

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CHAPTER 5

GASTROCNEMIUS MEDIALIS MUSCLE GEOMETRY AND EXTENSIBILITY IN TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH SPASTIC PARESIS AGED 6 TO 13 YEARS

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ABSTRACT

The aim of this cross-sectional study is to compare gastrocnemius medialis muscle (GM) geometry and extensibility between children with spastic cerebral paresis (SCP) and typically developing (TD) children. In addition, we aim to evaluate if, and how alterations in GM geometry relate to GM extensibility.

Thirteen children with SCP (mean age 9.7 ± 2.1 years; GMFCS: I-III) and fourteen TD children (mean age 9.3 ± 1.7 years) participated in this study. GM geometry was assessed using 3D ultrasound imaging at 0 Nm and 4 Nm externally imposed dorsal flexion moments. GM extensibility was defined as the absolute length change of the GM muscle-tendon complex between the externally applied 0 and 4 Nm moments.

No differences in anthropometric variables and GM extensibility were shown between the SCP and TD groups. Although GM muscle volume correlated with body mass in both groups, slopes of the regression line were substantially higher in TD compared to SCP (TD=3.3 ml/kg; SCP=1.3 ml/kg, $p<0.01$). In contrast to TD, GM fascicle length in children with SCP did not correlate with either age, lower-leg length or body mass. However, increases in GM physiological cross-sectional area as a function of body mass was not different between SCP and TD children (TD=38.9 mm^2/kg; SCP=58.7 mm^2/kg, $p=0.83$). We found that increases in length of tendinous structures, i.e. summed tendon and aponeuroses lengths as a function of lower-leg length, in children with SCP exceeded increases found in TD children (TD=0.85 cm/cm; SCP=1.16 cm/cm, $p<0.01$), and even exceeded lower-leg length increases. In addition, in children with SCP, GM extensibility correlated negatively with body mass ($r= -0.61$), height ($r= -0.66$), muscle volume ($r= -0.66$), physiological cross-sectional area ($r= -0.59$), and tendon length ($r= -0.68$). Such negative relations were not found in TD children.

In conclusion, this study shows that the relations between GM morphology and GM extensibility differs between children with SCP and TD children.

INTRODUCTION

Spastic paresis (SCP) is a common neuromuscular disorder either inherited or caused by brain lesions during development. Children with SCP, particularly when the disorder affects the lower leg, often develop equines gait, which is characterised by ankle plantar flexion in the stance phase and limited push-off power (Ballaz et al., 2010; Voorman et al., 2007; Gage, 2009; Dallmeijer et al., 2011). Without treatment, gait and ankle range of motion (ROM) impairments typically worsen with age (Nordmark et al., 2009; Beckung et al., 2007). Clinical interventions often involve a combination of physiotherapy, orthoses, serial casting, Botulinum NeuroToxin-A (BoNT-A) intramuscular injections, intrathecal baclofen administration, selective dorsal rhizotomy, and/or orthopaedic surgery (Koman et al., 2004). Although above-mentioned interventions improve ankle ROM on the short-term (Nieuwenhuys et al., 2016), recurrence on the long-term has frequently been reported (Fry et al., 2007; Tedroff et al., 2009; Spijker et al., 2009).

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Increased resistance to ankle dorsal flexion (ankle joint hyper-resistance) is an often encountered problem in children with SCP. Ankle joint hyper-resistance to dorsal flexion is predominantly reported to be related to increased triceps-surae hyper-resistance (van den Noort et al., 2017). This muscular hyper-resistance primarily relates to disturbances in muscle excitation in SCP, such as hyperreflexia and involuntary background excitation (van den Noort et al., 2017). Secondary to these disturbances in muscle excitation, muscle hyper-resistance is influenced by changes in morphological characteristics. In animal experiments, muscle geometric characteristics have been shown to be major determinants of active and passive length-force characteristics (Woittiez et al., 1983). Geometrical characteristics of the gastrocnemius medialis muscle (GM) have been investigated extensively in animal and human studies (Huijing, 1985; Zuurbier & Huijing, 1993). Studies in children with SCP have shown that GM volume normalised for body mass is on average around 22% smaller than in TD children (Barber et al., 2011b, 2016). Such reduced GM volumes may be related to relatively shorter fascicles (Mohagheghi et al., 2008; Barber et al., 2011a) and/or smaller physiological cross-sectional areas (A_{fasc}) (Malaiya et al., 2007; Lieber et al., 2003; Barber et al., 2011a). In turn, short fascicles and a small physiological cross-sectional area will likely affect the active and passive range of force exertion of the muscle. In particular, shorter fascicles reduce both the length range of active force exertion and extensibility. On the other hand, a smaller A_{asc} is related to reduced optimum force and increased muscle extensibility.

To date, most studies examining the anatomy of the GM have focused on the muscle belly (see for review: Barrett & Lichtwark, 2010). The tendinous structures, and their relation to muscle belly characteristics, have not been studied extensively.

Therefore, it is not well understood how altered GM geometry in children with SCP affects ankle dorsal flexion hyper-resistance. Most comparisons of morphological determinants of limited ankle-hyper resistance in children with SCP have been based on group differences, concealing age related individual variations within groups. Thus, more insight in the development of GM geometry in typically (TD) developing children and in children with SCP is needed.

In TD children, GM growth is related to uniform increases in physiological cross-sectional area, fascicle and tendon length (Bénard et al., 2011). In order to understand the underlying mechanisms of ankle joint hyper-resistance in children with SCP, estimates of such GM morphological variables in children with SCP, and their relation to age, body dimensions and GM extensibility are required. The aim of this study is to compare GM geometry and GM extensibility between children with SCP and TD children. In addition, we aim to evaluate if and how alterations in GM geometry relate to GM extensibility.

METHODS

Participants

Thirteen children between the age of 6 and 13 years with uni- or bilateral spastic paresis (SCP) (GMFCS I-III) were selected from a population visiting the Amsterdam University Medical Centre (location VUmc, Amsterdam, the Netherlands). Children were excluded if they had undergone any neurosurgery or orthopaedic surgery of the lower limb at all or chemical denervation (Botulinum NeuroToxin-A) less than six months prior to the measurements. A convenience sample of 14 typically developing children (TD) in the same age range as the children with SCP participated as controls. For both groups, we excluded children if they had other diseases affecting the musculoskeletal system. Before taking part, written informed consent from both parents and verbal consent from participants were received. The study was approved by the medical ethics committee of the Amsterdam University Medical Centre. For all subjects, measurements were performed by the same assessor (GW). In the SCP group, measurements were performed on the leg with the most resistance against ankle dorsal flexion, as assessed during a clinical physical examination. In the TD group, we selected the right leg.

Anthropometry

Body mass and height were measured. Lower leg length was approximated as the mean of distances measured medially and laterally from the most prominent point on each femur epicondyle to the most prominent point of the corresponding malleolus.

Electromyography

During morphology measurements, surface electromyographies (EMG) of m. gastrocnemius lateralis (GL, because of inaccessibility of GM) and m. tibialis anterior (TA) were assessed to quantify muscle excitations of agonistic and antagonistic muscles around the ankle. Preparation of the skin and placements of EMG electrodes were performed according to SENIAM guidelines (Hermens et al., 2000), and by determining the outline of the muscles using ultrasound (Hermens et al., 1999). A multichannel system (MOBI, TMS-International, The Netherlands) was used to sample EMG signals at 1024 Hz.

Prior to the measurements, participants were asked to perform a 5-seconds isometric maximal voluntary contraction (MVC) against resistance (applied by the assessor), towards both dorsal and plantar flexion. During assessment of ankle moment-angle relation and GM geometry, excitations of GL and TA were confirmed to be well below the a priori set inclusion limit of 10% MVC (Bénard et al., 2010). Note that the actual experimental value of this variable (mean≈2.2% MVC) is quite low. Therefore, it is concluded that any alterations in GM geometry, observed between groups, should be ascribed to factors other than muscle excitations.

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Foot plate angles corresponding to externally exerted moments

Subjects were asked to lie prone on the examination table with both feet hanging over the edge. The dorsal flexion foot plate angle was set using a custom-designed apparatus (Bénard et al., 2010), comprising an adjustable foot plate and a torque wrench, equipped with an inclinometer (further referred to as the inclino-dynamometer). The inclino-dynamometer can be connected to the foot plate. Similar to the stabilization procedure of the foot during physical examination, and during the fitting of ankle-foot orthoses, this custom foot plate allows adjustments targeted to stabilise the subtalar joint as much as possible during foot sole rotations (Huijing et al., 2013). In short the procedure consists of the following steps: 1) Positioning of the calcaneus in a neutral position under the tibia; 2) Adduction of the forefoot until the midline of the calcaneus points between 2nd and 3rd ray of the forefoot; 3) Applying additional fore and mid-foot supination until no movement within the subtalar joint can be detected by palpation (Huijing et al., 2013). Foot plate rotations were set by exerting external moments corresponding to 0 Nm and 4 Nm dorsal flexion. These moments were applied and quantified at the interface between the foot plate and the torque wrench.

GM morphometry

Morphological characteristics were collected at specific foot plate rotations corresponding to standardised externally applied moments (i.e. 0 Nm and 4 Nm), using an extendable rod to connect the foot plate to the table. During the

3D ultrasound examination, a 5 cm linear probe (Technos MPX, ESAOTE S.p.A. Italy) was moved (swept) in a transverse orientation with respect to the leg, in a longitudinal direction over the skin, superficial to the GM. For most subjects multiple sweeps were required to capture the entire GM (Weide et al., 2017). Location and orientation of the probe were registered by a motion capture system (Optotrak 3020, NDI, Waterloo, Canada), and were synchronised with ultrasound images to construct a three-dimensional voxel array, i.e. 3D ultrasound image, using custom software (Matlab, Mathworks Co, Natick, Massachusetts, USA) (Weide et al., 2017).

Analysis of 3D ultrasound images was performed using newly adapted methods (Weide et al., 2017), yielding improvement compared to those used previously by our group. Coordinates of the GM insertion on the calcaneus, the most distal end of GM muscle belly, and the estimated coordinates of the GM origin on the medial femur condyle (for anatomical details see (Bénard et al., 2010)) were assessed from the 3D ultrasound images using the freeware medical imaging interaction toolkit (MITK, www.mitk.org). Based on the distances between these coordinates, muscle belly length (ℓ_{m}), tendon length (ℓ_{t}), and muscle-tendon complex (ℓ_{m+t}) were calculated (Fig. 1). GM muscle volume (V_{GM}) was measured between the origin and distal end of the muscle belly using manual segmentation of the anatomical cross-sections and subsequent interactive interpolation in MITK. Fascicle length (ℓ_{fasc}) and pennation angles (α_{fasc}) were measured within the mid-longitudinal fascicle plane at a position $^{2}/_{3}$ along the muscle belly (from origin) (Fig. 1). Physiological cross-sectional area (A_{fasc}) was calculated by dividing muscle volume by ℓ_{fasc}. Aponeurosis length (ℓ_{a}) was estimated according to the law of cosines of the right triangle constructed by the variables ℓ_{fasc}, ℓ_{m}, and α_{fasc} (eq. 1, Fig. 1).

$$\ell_{a}^{2} = \ell_{fasc}^{2} + \ell_{m}^{2} - 2 * \ell_{fasc} * \ell_{m} * \cos(\alpha_{fasc}) \qquad (1)$$

Together the tendon and aponeurosis represent the tendinous structure or the major part of the-series elastic component of GM muscle-tendon complex. We used the summed lengths of these structures (ℓ_{a+t}) as a variable. The extensibility of the total muscle-tendon complex was defined as the absolute change in ℓ_{m+t} between the 0 Nm to 4 Nm conditions.

Statistical Analysis

Two types of statistics were used:

I. TD-SCP group comparisons using means and standard errors.

Student's t-tests were used to test for significance of differences between mean values of SCP and TD groups regarding age, body mass, body height, lower-leg length and GM geometrical characteristics measured at 0 Nm. To test for differences in (normalised) morphological characteristics between groups, a two-way mixed ANOVA with between-subject factor (group) and within-subject factors (externally applied moments: 0 Nm and 4 Nm) was used to test for main- and interaction effects between groups.

II. Regression analysis using individual data of subjects.

Pearson's product-moment coefficients of correlations and linear regressions were used to assess relations between age, and geometrical and anthropometric characteristics, using individual data. Differences in slopes were tested using Sigma Plot (Version 12.0, Systat Software, San Jose, CA).

For Student's t-tests, ANOVA and Pearson's correlations we used SPSS (version 25.0, SPSS Inc.,2018), with the level of significance set at $p < 0.05$.

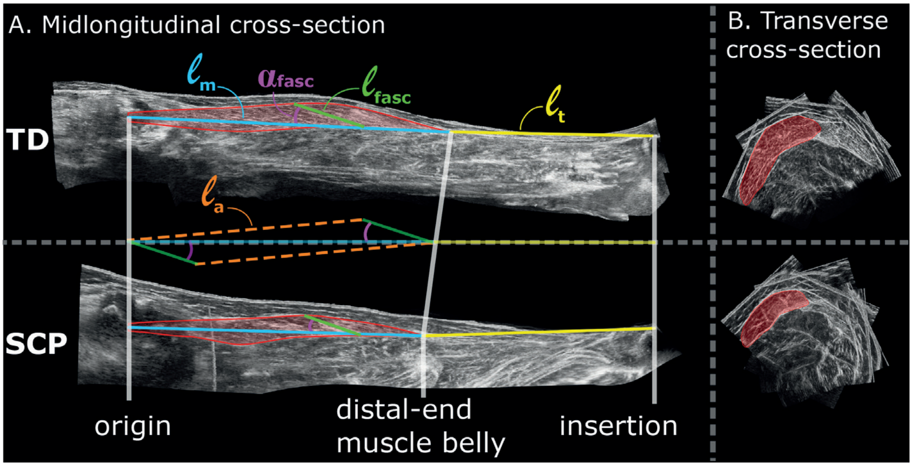

Figure 1. Examples of lower leg 3D ultrasound images from TD (top) and SCP (bottom) children. A) left panels show the mid-longitudinal fascicle plane of the gastrocnemius medialis muscle from which fascicle parameters are assessed. Assessments of morphological characteristics are shown as a coloured overlay on top of the mid-longitudinal 3D ultrasound image. ℓ_m = muscle belly length, ℓ_t = tendon length, α_{fasc} = pennation angle, ℓ_{fasc} = fascicle length and ℓ_a = aponeurosis length. **B)** Right panels show 3D ultrasound images of transverse cross-sections of the GM, hallway along the longitudinal axis of the muscle belly. Red area indicates segmented anatomical cross-section area of the GM from which multiple segmentation along the longitudinal axis of the muscle belly are drawn to estimate muscle volume.

RESULTS

Participant characteristics

There were no differences in age or anthropometric variables between the SCP and TD group (Table 1). Body mass increased with increasing lower-leg lengths in both SCP and TD (by 2.1 kg cm^{-1} and 2.0 kg cm^{-1} increase in lower leg-length, respectively).

Comparisons of GM geometry of SCP and TD groups

Since one child with SCP moved during the 3DUS imaging procedure, muscle volume could not be measured reliably, and thus V_{GM} and A_{fasc} could not be determined for this child.

Absolute GM geometry (at 0 Nm): SCP-TD comparison

Measured at 0 Nm, muscle volume (V_{GM}) was on average 47% smaller (-39.6 ml) in children with SCP compared to TD children (Table 1). Absolute muscle belly length (ℓ_{m}) and fascicle length (ℓ_{fasc}) in the SCP group were smaller (by -2.8 cm or -14%, and -1.2 cm or -23% respectively) compared to the TD group, as measured at 0 Nm. However, no significant differences could be shown for absolute values of muscle-tendon complex length (ℓ_{m+t}), physiological cross-sectional area (A_{fasc}), fascicle pennation angle (α_{fasc}), tendinous structures (ℓ_{a+t}), aponeurosis length (ℓ_{a}), and tendon length (ℓ_{t}) measured at 0 Nm (Table 1).

Normalised GM geometry (0-4 Nm): SCP-TD comparison

After normalization for lower leg length, ANOVA of length variables measured at 0 Nm and 4 Nm showed that normalised muscle-tendon complex length ($\ell_{m+t/}\ell_{lowerleg}$) and normalised aponeurosis length ($\ell_{a/}\ell_{lowerleg}$) were still not different between groups. However, in SCP normalised muscle belly length ($\ell_{m/}\ell_{lowerleg}$) was 9.4% shorter and normalised tendon length ($\ell_{t/}\ell_{lowerleg}$) 13.3% longer compared to those in the TD group (Fig. 2, lines with # indicate the main effects for group differences). In addition, normalised fascicle length ($\ell_{fasc/}\ell_{lowerleg}$) was 18.8% shorter in SCP compared to TD. Compared to TD, these results show that after the adjustment for lower leg length differences, muscle-tendon complexes in children with SCP seem to be comprised of a shorter muscle belly, with shorter fascicles, and a longer tendon.

Effects of increased applied ankle dorsal flexion moments on GM geometry

In both groups, upon exerting 4 Nm dorsal flexion $\ell_{m+t/}\ell_{lowerleg}$ increased by 2.8% and $\ell_{m/}\ell_{lowerleg}$ increased by 3.2% (Fig. 2). In addition, in both groups $\ell_{fasc/}\ell_{lowerleg}$ increased by 2.5%, and α_{fasc} decreased by 1.4 degrees similarly. However, in neither of the groups, changes of $\ell_{t/}\ell_{lowerleg}$ and $\ell_{a/}\ell_{lowerleg}$ were found.

There were no interaction effects of group and condition (i.e. between the 0 Nm to 4 Nm conditions). These findings indicate that changes in GM geometry in response to externally applied ankle dorsal flexion were not different between groups.

Table 1. Variables of age, subject characteristics and gastrocnemius medialis muscle geometry (at 0 Nm) and their correlation with age.

	Mean ± SE		Coefficient of correlation r with age	
Variables	**TD**	**SCP**	**TD**	**SCP**
Age (years)	9.3 ± 0.5	9.7 ± 0.6	N.A	N.A.
Body mass (Kg)	33.2 ± 2.4	33.2 ± 2.7	0.83#	0.6#
Body height (cm)	140.5 ± 3.8	136.8 ± 3.5	0.88#	0.72#
Lower leg length (cm)	32.8 ± 1.2	31.2 ± 1.1	0.79#	0.66#
Body mass index (-)	16.5 ± 0.4	17.4 ± 0.7	0.5	0.34
Sex (# Males/#Females)	5 / 9	7 / 6	N.A.	N.A.
# GMFCS per category	N.A.	I=3, II=9, III=1	N.A.	N.A.
V_{GM} (ml)	91.8 ± 8.0	52.3 ± 4.1*	0.75#	0.45
A_{fasc} (cm^2)	17.0 ± 1.0	13.8 ± 1.8	0.59#	0.48
ℓ_{fasc} (cm)	5.3 ± 0.2	4.1 ± 0.2*	0.84#	-0.17
α_{fasc} (deg)	13.5 ± 0.4	13.9 ± 1.0	-0.37	0.45
ℓ_{m+t} (cm)	34.7 ± 1.2	33.0 ± 1.2	0.86#	0.69#
ℓ_{a+t} (cm)	29.6 ± 1.0	29.0 ± 1.3	0.82#	0.69#
ℓ_m (cm)	20.3 ± 0.7	17.5 ± 0.7*	0.77#	0.37
ℓ_t (cm)	14.4 ± 0.6	15.5 ± 0.9	0.79#	0.67#
ℓ_a (cm)	15.2 ± 0.5	13.6 ± 0.8	0.70#	0.40

*indicates a significant difference between SCP and TD ($p < 0.05$), # indicates a significant correlation with age ($p < 0.05$). These symbols indicate the following V_{GM}= muscle volume, A_{fasc}= physiological cross-sectional area, ℓ_{fasc}= fascicle length, α_{fasc}= pennation angle, ℓ_{m+t}= muscle-tendon complex length, ℓ_{a+t}: tendinous structure length, ℓ_m= muscle belly length, ℓ_t= tendon length, ℓ_a= aponeurosis length.

Absolute GM extensibility (0-4 Nm): SCP-TD comparison

Between groups, no difference was shown for extensibility of GM muscle-tendon complex ($\Delta\ell_{m+t}$=0.86 cm in TD, $\Delta\ell_{m+t}$=0.90 cm in SCP). However, increased variation in extensibility in the SCP compared to the TD group (coefficient of variation of 37% in SCP and 33% in TD) indicates a somewhat enhanced heterogeneity in the SCP group.

To avoid effects of imposing different length conditions of variables (e.g. muscle-tendon complex lengths, muscle belly length, tendon length, fascicle length, or sarcomere lengths) between groups, ideally, we should have made group comparisons at similar length conditions. However, Fig. 3 shows large individual variation in normalised muscle and tendon lengths measured at 0 Nm and 4 Nm, yielding overlap for similar lengths conditions only for a limited number of subjects. This, by itself, makes the intended identification of underlying mechanisms of limited extensibility impractical. It also means we should interpret the results of group comparisons above with the utmost care.

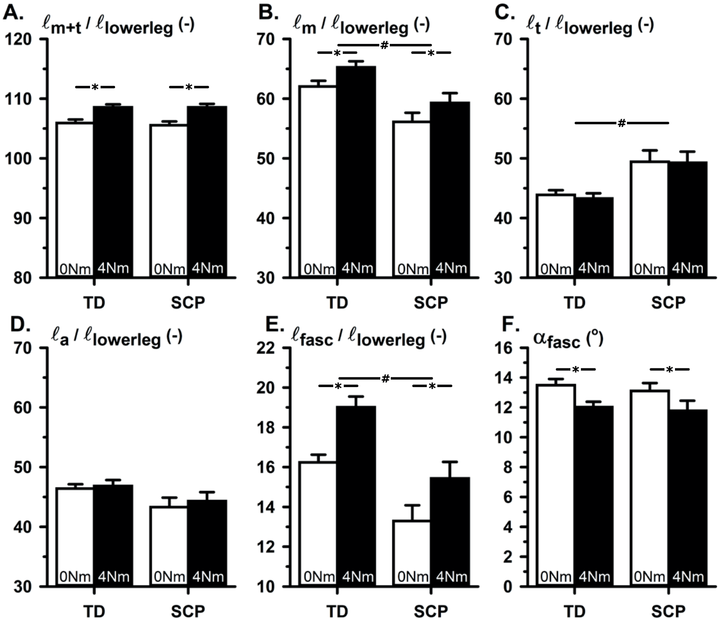

Figure 2. TD-SCP comparison of normalised values of elements of GM muscle belly and tendon geometry corresponding to 0 Nm as well as 4 Nm externally applied dorsal flexion moments. **A)** $\ell_{m+t}/\ell_{lowerleg}$= summed lengths of muscle belly and tendon normalised for lower leg length. **B)** $\ell_m/\ell_{lowerleg}$= muscle belly length normalised for lower leg length. **C)** $\ell_t/\ell_{lowerleg}$= tendon length normalised for lower leg length. **D)** $\ell_a/\ell_{lowerleg}$= aponeurosis length normalised for lower leg length. **E)** $\ell_{fasc}/\ell_{lowerleg}$= fascicle length normalised for lower leg length. **F)** α_{fasc}= pennation angle in degrees between fascicle and longitudinal axis of the muscle belly. Significance is indicated; * p <0.05 for a main effect of condition (externally applied dorsal flexion moments), # p <0.05 for a main effect of group (TD-SCP).

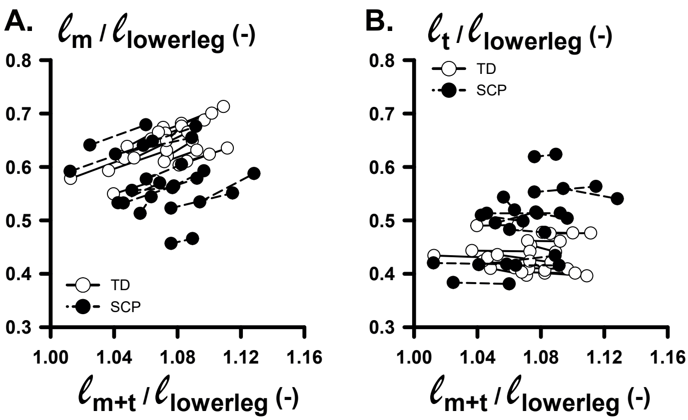

Figure 3. Changes in normalised muscle and tendon lengths as functions of normalised muscle-tendon complex lengths corresponding to externally applied 0-4Nm dorsal flexion moments. A) Plot relating $\ell_m/\ell_{lowerleg:}$ (muscle belly length normalised for lower leg length) with $\ell_{m+t}/\ell_{lowerleg}$ (summed lengths of muscle belly and tendon, normalised for lower leg length) measured at 0 Nm and 4 Nm dorsal flexion moment. **B)** Plot relating $\ell_t/\ell_{lowerleg:}$ (tendon length normalised for lower leg length) with $\ell_{m+t}/\ell_{lowerleg}$, measured at 0 Nm and 4 Nm dorsal flexion moment. Solid line and dashed lines links individual data between 0 Nm and 4 Nm for TD and SCP individuals, respectively.

Comparison of GM geometrical variables using individual children data

GM muscle-tendon complex length and its constituents (at 0 Nm)

Regression analyses of muscle-tendon complex length (ℓ_{m+t}) with ℓ_{fasc}, and ℓ_{a+t} showed that in TD children, ℓ_{fasc} significantly and positively correlated with ℓ_{m+t}. However, no such correlation was found for children with SCP. In both TD and SCP, ℓ_{a+t} correlated positively with ℓ_{m+t}. These results show that at 0 Nm for children with SCP, longer muscle-tendon complex lengths are accompanied by longer tendons, but not by longer muscle fascicles, as was shown for TD children.

GM muscle volume and its constituents (at 0 Nm)

Regression analyses of GM muscle volume with its constituents ℓ_{fasc} and A_{fasc} showed that in TD, ℓ_{fasc} is significantly and positively correlated with V_{GM} (Fig. 4A). However, no such correlation was found for children with SCP. In both TD and SCP, A_{fasc} was positively correlated with V_{GM} (Fig. 4B). As one outlying data point may have contributed considerably to these correlations for children with SCP, however correlation analysis without this data point was still significant for children with SCP (r=0.89).

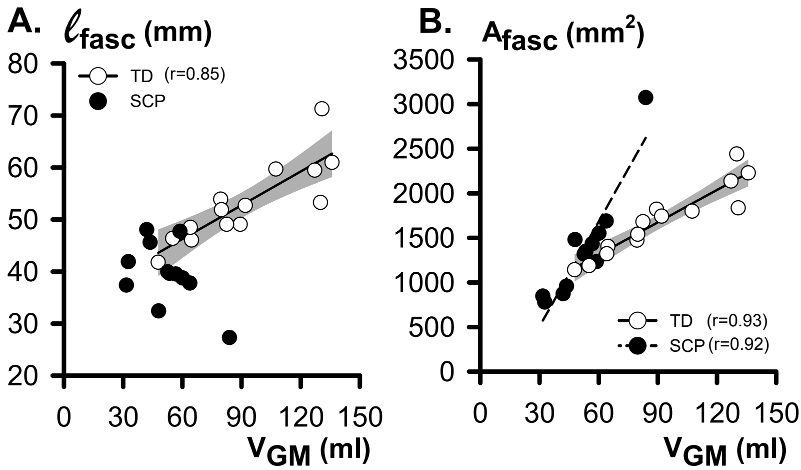

Figure 4. Regression analysis of morphological GM belly characteristics as functions of GM (at 0 Nm). A) Plot relating individual ℓfasc (fascicle length) and VGM (muscle volume) data. Note that exclusively for TD children, a significant and positive correlation was shown. **B)** Plot relating individual A_{fasc} (physiological cross-sectional area) and VGM data. Note the positive correlation, indicating that in both the TD and SCP group, children with a big VGM also have a larger A_{fasc}. The shaded area represents the 95% confidence interval for the TD group. No regression line is drawn and no coefficient of correlation is indicated for data not showing a significant coefficient of correlation.

Relations between structures constituting the GM geometry: SCP-TD comparison

In both TD and SCP children, age affected GM geometry (Table 1). In TD children, V_{GM} increased with age by 13.3 ml year^{1}, A_{fasc} by 134 mm^{2} year^{-1} and ℓ_{fasc} by 3.8 mm year^{-1}. However, no significant increases of V_{GM}, A_{fasc}, and ℓ_{fasc} with age were found for children with SCP (Fig. 5, Table I). Muscle-tendon complex length correlated with age in both TD and SCP in a similar way (by 2.2 cm year^{-1} in TD and 1.5 cm year^{-1} and SP respectively). Tendon length (ℓ_t) increased with age in both TD and SCP similarly (by 1.0 cm year^{-1} in TD and 1.0 cm year^{-1} in SCP). Although, muscle belly length and aponeurosis length increased in TD with age (increase by 1.2 cm year^{-1}, and by 0.78 cm year^{-1}, respectively), no such correlations were found in children with SCP. Thus, muscle-tendon complex characteristics in TD children are explained by age-related changes of both ℓ_m and ℓ_t, whereas in children with SCP, these characteristics can only be explained by age-related changes in ℓ_t. The length of the tendinous structures (ℓ_{a+t}) increased with age in both TD and SCP similarly (by 1.8 cm/year^{-1} in TD and 1.6 cm year^{-1} in SCP) (Fig. 5 D).

To assess whether GM geometry and its constituents correlated with lower leg length and body mass, we plotted these morphological characteristics as a function of lower leg length and body mass (Fig. 6). In TD children and children with SCP, muscle volume increased with body mass differently (Fig. 6A; increases by 3.3 ml kg^{-1} in TD and 1.3 ml kg^{-1} in SCP). In both TD and SCP, A_{fasc} increased as a function of body mass similarly (by 38.9 mm^2 kg^{-1} in TD and by 58.7 mm^2 kg^{-1} in SCP). For TD children, ℓ_{fasc} increased as a function of lower-leg length by 0.14 cm cm^{-1}. However, no correlation was found for children with SCP (Fig. 6C). In both TD and SCP, ℓ_{a+t} increased as a function of lower leg length differently (by 0.85 cm cm^{-1} in TD and 1.16 cm cm^{-1} in SCP). Thus, length increases of tendinous structures in children with SCP exceeded that of TD children. In addition, length increases of the tendinous structures exceeded increases in lower leg length exclusively in children with SCP.

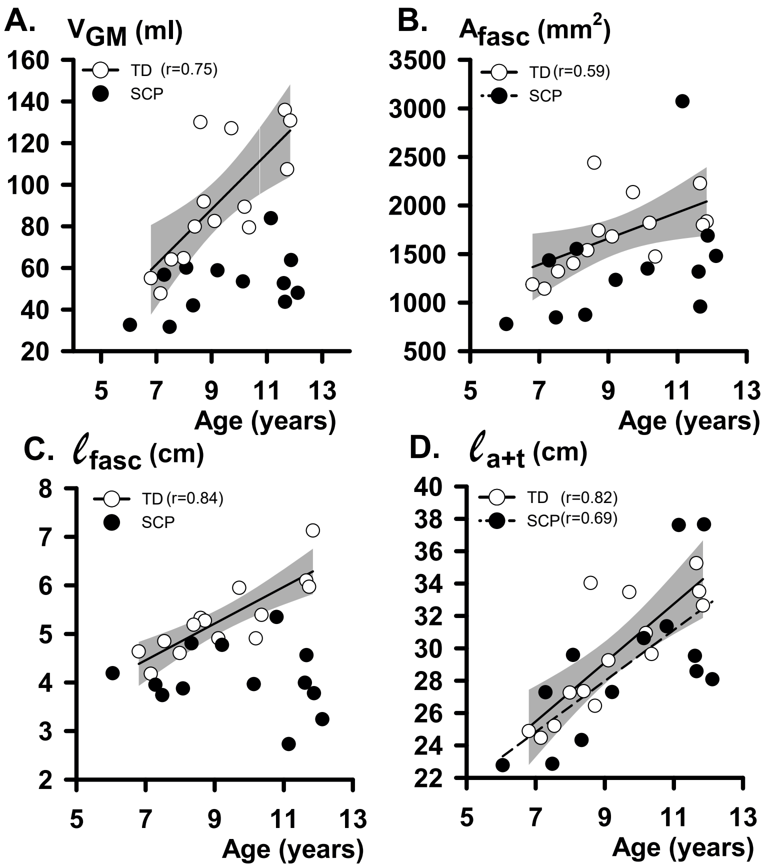

Figure 5. Regression analysis of individual geometrical characteristics of GM muscle and age data. A) Plot relating individual V_{GM} (muscle volume at 0 Nm) to age. **B)** Plot relating individual A_{fasc} (physiological cross-sectional area at 0 Nm) to age. **C)** Plot relating individual ℓ_{fasc} (fascicle length at 0 Nm) to age. **D)** Plot relating individual ℓ_{a+t} (tendinous structure length at 0 Nm) to age. The shaded area represent the 95% confidence intervals for the TD children. No regression line is drawn and no coefficient of correlation is indicated for data not showing a significant coefficient of correlation.

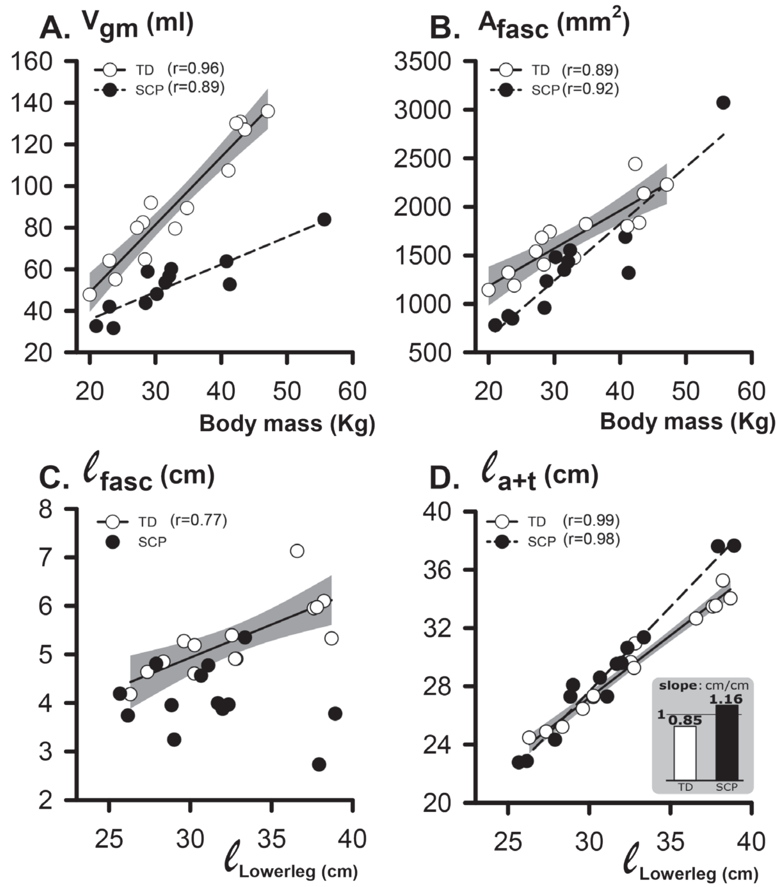

Figure 6. Regression analysis of individual geometrical characteristics of GM muscle and body mass or lower leg length. A) Plot relating individual V_{GM} (muscle volume at 0 Nm) to body mass data. **B)** Plot relating individual A_{fasc} (physiological cross-sectional area at 0 Nm) to body mass data. **C)** Plot relating individual ℓ_{fasc} (fascicle length at 0 Nm) to lower leg length data. **D)** Plot relating individual ℓ_{a+t} (i.e. tendinous structure length at 0 Nm) to lower leg length data. The inset bar graph illustrates the significant difference in slope ($\ell_{a+t}/\ell_{lowerleg}$) between children with SCP and TD children. The shaded area represents the 95% confidence interval for the TD group. No regression line is drawn and no coefficient of correlation is indicated for data not showing a significant coefficient of correlation.

Relations of anthropometric and GM geometric variables to GM extensibility

For both groups, we found no significant correlations of muscle-tendon complex extensibility with age (see Table 2). This indicates that absolute muscle-tendon complex extensibility does not change with age. However, we did find negative correlations between anthropometric variables and muscle-tendon complex extensibility, except for lower leg length. However, no such correlations between anthropometric values and muscle-tendon complex extensibility were found in TD children (Table 2). These findings indicate that exclusively in children with SCP increases in body size are associated with decreases in absolute muscle-tendon complex extensibility.

Analysis of individual data show that, in children with SCP, a hypothetical 1 mm decrease in GM extensibility is correlated to the net effect of increases in GM muscle volume (by 27.98 ml), A_{fasc} (by 1189.38 mm^2), and length of tendinous structures (by 8.3 cm). In contrast, GM extensibility in TD children was positively correlated to A_{fasc}. Besides A_{fasc}, no other GM geometric variable showed a significant correlation with GM extensibility in TD children. These results show that growth related increases of GM geometry in children with SCP are associated with a decrease in GM extensibility.

Table 2. Coefficients of correlation of anthropometric variables and muscle geometrical variables at 0 Nm with muscle-tendon extensibility.

Variables	**Coefficient of correlation r with extensibility**	
	TD	**SCP**
Age	0.25	-0.35
Body mass	0.36	-0.61$^{\#}$
Body height	0.50	-0.66$^{\#}$
Lower leg length	0.51	-0.52
V_{GM}	0.51	-0.66$^{\#}$
A_{fasc}	0.59$^{\#}$	-0.59$^{\#}$
ℓ_{fasc}	0.33	0.44
α_{fasc}	-0.19	-0.55
ℓ_{m+t}	0.43	-0.54
ℓ_{a+t}	0.43	-0.59$^{\#}$
ℓ_{m}	0.41	-0.10
ℓ_{t}	0.36	-0.68$^{\#}$
ℓ_{a}	0.42	-0.22

Significance is indicated; $^{\#}$ $p < 0.05$. These symbols indicate the following $\mathbf{V_{GM}}$= muscle volume, $\mathbf{A_{fasc}}$=physiological cross-sectional area, $\ell_{\mathbf{fasc}}$= fascicle length, $\alpha_{\mathbf{fasc}}$= pennation angle, $\ell_{\mathbf{m+t}}$= muscle-tendon complex length, $\ell_{\mathbf{a+t}}$= tendinous structure length, $\ell_{\mathbf{m}}$= muscle belly length, $\ell_{\mathbf{t}}$= tendon length, $\ell_{\mathbf{a}}$= aponeurosis length. Muscle-tendon complex extensibility is defined as the absolute change in muscle-tendon complex length from 0 Nm to 4 Nm dorsal flexion.

DISCUSSION

Our cross-sectional study shows that the GM geometry of children with SCP is mainly characterised by smaller muscle bellies, related to a limited or absent longitudinal fascicle growth. In addition, we found that exclusively in children with SCP, growth related length increases of tendinous structures exceeded that of lower leg length. Only in children with SCP, we found a negative coefficient of correlation of both the physiological cross-sectional area and length of tendinous structures with muscle-tendon complex extensibility. These results show how, at least part of, the triceps-surae muscle hyper-resistance to extension in children with SCP can be explained by growth-related adaptations of the GM.

Limitations of the present study

Given the design of the present study, we cannot isolate and therefore distinguish separate mechanisms responsible for the acute increases of fascicle length or any other structure in children with SCP. It is conceivable that at the exertion of the standardised applied foot plate moments, even if there were no changes in GM geometry, limitations of joint movement may be caused by combined changes within or outside the GM. This may prevent attainment of higher fascicle lengths at 0 Nm than those presently found. Limitations concerning the 3D-ultrasound and inclino-dynamometer technique were described and discussed previously (Bénard et al., 2011, 2010, 2009; Weide et al., 2017, 2015).

Group comparisons

Studies using ankle-dynamometry measurements and gait analysis show more plantar flexed feet in children with SCP compared to TD children, suggesting short muscle-tendon complexes (Singer et al., 2002; Tardieu et al., 1982; Harlaar et al., 2000). In contrast to such studies, we refer to foot sole angles rather than to ankle joint angles, as we have clear indications that foot flexibility confounds the comparison of GM geometry between groups at similar foot sole (Chapter 4) (Huijing et al., 2013). Ideally, comparisons of GM geometry should be made at a comparable muscle-tendon complex length. Since no *in-vivo* approach is available to make such comparisons, comparisons of GM geometry were standardised to similar external conditions, e.g. “resting” foot sole angle or externally applied moment. Differences in standardization approach most likely underlie the ambiguity concerning fascicle length in children with SCP, since both shorter (Wren et al., 2010) and similar (Schless et al., 2018) muscle-tendon complex lengths have been reported for SCP groups. In the present study, there was no difference in muscle-tendon complex length between SCP and TD groups.

In accordance with other studies that quantified GM geometry at “resting” ankle joint angles or 0 Nm conditions, we did find morphological characteristics such as muscle volume (Schless et al., 2018; Barber et al., 2011B; Noble et al., 2014; Pitcher et al., 2018), fascicle length (Mohagheghi et al., 2008; Matthiasdottir et al., 2014; Gao et al., 2011), and physiological cross-sectional area (Barber et al., 2011B, A) to be smaller, and tendon length (Barber et al., 2012) to be larger in the SCP compared to the TD group. However, also in the literature, several studies found similar fascicle lengths at this so-called “resting” joint angle in the SCP compared to the TD group (Barber et al., 2011A, B; Malaiya et al., 2007; Shortland et al., 2004, 2002; Wren et al., 2010). Conclusions regarding growth based on group differences may deviate from conclusions based on regression analysis that considers individual variations. This can be exemplified by the study of Malaiya et al., 2007, who studied muscle growth in children with SCP and allowed further interpretation due to the transparent and extensive description of their methods and results. Based on group comparison, Malaiya et al. (2007) argued that reduced muscle growth in children with SCP is only related to reduced physiological cross-sectional area growth, and not to reduced longitudinal fascicle growth. However, other parts of that same study may lead to different conclusions (see below).

5

SCP-TD comparison based on individual data

Similar growth of body dimensions in SCP and TD children

Differences in body dimensions between children have been reported (e.g. Grammatikopoulou et al., 2009; Tomoum et al., 2010; Walker et al., 2015; Herskind et al., 2016). In contrast, both body dimensions and growth thereof did not differ between our samples of children with SCP and TD children. This may be due to the limited group size and relatively mildly affected children with SCP, as GMFCS levels in SCP correlate with smaller body dimensions (Walker et al., 2015; Wang et al., 2016).

Less muscle volume growth in children with SCP compared to TD

In line with the previous studies (Noble et al., 2014; Willerslev-Olsen et al., 2018; Herskind et al., 2016), our results show that GM muscle volume increases with body mass in children with SCP, though at a lower rate compared to TD children. Note, however, that at larger body masses children with SCP attain considerably smaller GM muscle volumes than TD children, as the slopes of the regression lines of SCP and TD children are very different. In agreement with previous results of Herskind et al. (2016), at similar body mass (≈20 kg in their Fig. 1), GM muscle volume is smaller, but the differences seem relatively small. In addition, Herskind et al. (2016) reported that GM muscle volume in children with SCP deviates substantially from TD children at the age of 15.5 months, which is the age at which children typically start to walk. This substantial deviation in GM muscle volume is surprising, considering the relatively small difference in GM muscle volume at ≈20 kg (≈5 years of age). This suggests that, during development, children with SCP are capable of catching up with TD children on the aspect of GM muscle volume growth. Further work on this topic seems desirable.

Increases of GM tendinous structures in SCP and TD children.

Particularly at higher ages, or larger lower leg lengths, the tendinous structure in children with SCP is relatively longer than in TD children. This is emphasised by the observation that increases in tendinous structure lengths exceeded increases in lower leg length exclusively in children with SCP. A similar effect, namely increases in tendinous lengths being larger than bone growth, is also seen following an experimental transfer of the flexor carpi-ulnaris distal tendon to the extensor site in healthy animals (Maas & Huijing, 2012). Thus, our present results confirm indications of other studies (Tardieu et al., 1977; Wren et al., 2010), that factors other than lower leg length must be involved in regulating tendon growth in children with SCP.

Mechanisms responsible for the adaptation of tendinous structures potentially change with maturation. In young animals, it has been shown that the muscle-tendon complex adapts to immobilization by tendon length changes, without changes in the number of sarcomeres in series (Blanchard et al., 1985; Tardieu et al., 1977). However, in adult animals, the muscle-tendon complex adapts solely by changes in the number of sarcomeres in series (Wren, 2003; Blanchard et al., 1985; Tardieu et al., 1977). It has been suggested that at younger age, lengths of tendons adapt to minimise strain (Wren, 2003). Increasing the length of tendinous structures to reduce strain in children with SCP may be beneficial to allow more ankle joint movement in the short term. However, the capacity of tendon structures to adapt in such a way seems to diminish in adult age for unknown reasons (Blanchard et al., 1985). One explanation may be a decreasing expression of growth factors responsible for tendon growth in young children (Okamoto et al., 2005; Gumucio et al., 2015). Especially in children with SCP, higher concentrations of transforming growth factor beta (TGF-β1) have been shown within the muscle and in the serum compared to TD children and adults (Pingel et al., 2019; Von Walden et al., 2018; Grether et al., 1999; Lin et al., 2010). Such age-dependent tendon plasticity may explain why very early initiation of intervention (e.g. the Ponseti method (Radler, 2013) are successful, especially in young children preventing further aberrant adaptations.

If material properties of the tendinous structures and the cross-sectional area remain similar, it is expected that the overall structure compliance increases with an increase in slack length. However, our results show that tendon length in children with SCP correlates negatively with muscle-tendon complex extensibility. This finding indicates that during growth, tendon material properties change, and/or the length of tendinous structures increases. When stretching the muscle by applying an externally applied moment (4 Nm), we did not find [acute] increases in the summed length of tendinous structures, nor for tendon or aponeurosis separately, in both SCP and TD children. Even when exerting 0 Nm externally, non-zero stresses on the Achilles tendon, its aponeuroses, and on tendinous structures of antagonistic muscles are expected (Wu et al., 2012), so that these structures are on the stiff part of their length-force curves at 0 Nm and 4 Nm. Fast release experiments on maximally dissected animal muscles have shown that tendinous structures (rather than intra- fibre components) lengthen only by 4% from zero force to optimum muscle force (Morgan et al., 1978). Some simple and rough calculations may guide our expectations on this (see next paragraph).

Analysis of effects on tendinous extensibility in TD children

In a TD child with a tendinous structure length (ℓ_{a+t}) of ≈30 cm and an optimum active force of 510 N (17 cm^2 of A_{fasc} and a specific tension of around 30 N/cm^2 (Erskine et al., 2011; van der Zwaard et al., 2018)), we would expect to find 1.2 cm (4% of 30 cm) of tendon stretch. If dorsal flexion resistance to an external moment of 4 Nm should originate solely from GM, with an estimated moment arm ≈5 cm (Kalkman et al., 2017), it would result in a force pulling on the tendon with 80 N ($F = {}^{4}/_{0.05}$ N). Assuming a linear stress-strain curve, 80 N of force pulling on the tendon would result in 0.2 cm (${}^{80}/_{510}$*1.2) stretch of the tendinous structure. However, in reality other parallel arranged structures provide additional force transmission pathways, such as other plantar flexor muscles, joint capsules and ligaments, reducing the above estimated stress and strain of the GM tendinous structures. Thus, our finding of negligible acute increases in tendinous structures in response to the small and low range of externally applied moment meets our expectations.

Lower fascicle lengths attained in SCP compared to TD children

In our sample of children with SCP, age range 6-13 years, fascicle length expressed as functions of either age, lower leg length or muscle volume, deviates from those in TD children. However, differences in fascicle length between children with SCP and TD children were small at a lower age, shorter lower legs, and smaller muscle volumes. This is in agreement with the results of Herskind et al., 2016, who reported fascicle length of SCP and TD children up to five years old to increase indifferently. However, after this age, differences in fascicle length between SCP and TD increase with increases in age and lower leg length. Such a deviation is also reported in the study by Malaiya et al. (2007), (Fig. 3C: for children with SCP aged 4-12 years) that shows that in TD children, but not in children with SCP, individual fascicle length at “resting” foot angle correlates with fibula length. However, the finding that fascicle length only increases in TD seems underappreciated in their conclusion regarding GM muscle growth in children with SCP, stating that reduced GM growth is related to a reduced physiological cross-sectional area growth.

Reduced longitudinal fascicle growth in children with SCP may be related to reduced addition of sarcomeres in series, resulting in a smaller number of sarcomeres in series (Mathewson et al., 2015) and/or longer sarcomeres (Smith et al., 2011; Mathewson et al., 2015). Several mechanisms may be responsible for the comparatively reduced addition of sarcomeres in series in children with SCP (Von Walden et al., 2018; Dayanidhi & Lieber, 2014). Possibly in children with SCP, this may be due to effects of spasticity hindering typical muscle use and proliferation and differentiation of satellite cells (Dayanidhi & Lieber, 2014). Alternatively, enhanced longitudinal tendon growth in children with SCP (see above) may attenuate the stimulus for longitudinal fascicle growth.

Physiological cross-sectional area growth in SCP and TD children

In SCP and TD children, the physiological cross-sectional area of GM increases in a similar way with body mass. Such conclusions are also supported by Malaiya et al. (2007) after the reinterpretation of their data (Figs. 3A+C show that in children with SCP, GM muscle volumes increase without increases in fascicle length). Therefore, it can be concluded that in children with SCP, at least in the age range of 6-13 years, increases in muscle volume are mainly caused by increases in physiological cross-sectional area.

One may predict that increases in GM physiological cross-sectional area would negatively affect extensibility of the muscle-tendon complex, as more parallel arranged muscular material needs to be strained and may affect ankle range of motion (Weide et al., 2015). Understanding how different underlying mechanisms contribute to measured net extensibility is complex. For example, in our TD children, we found a positive coefficient of correlation between the physiological cross-sectional area and the muscle-tendon complex extensibility. This finding could imply that increases in the physiological cross-sectional area exclusively would cause increases in muscle-tendon complex extensibility. The negative effects of the increase of the physiological cross-sectional area on the extensibility may be compensated for by the simultaneous increase of fascicle length in TD children, which is not present in children with SCP.

Conclusions

In conclusion, age-related GM growth in children with SCP is characterised by increases in physiological cross-sectional area and in lengths of tendinous structures, without an increase in fascicle length. Our results show that in children with SCP, increases in GM muscle volume, physiological cross-sectional and lengths of tendinous structures are associated with a reduced GM extensibility, while such relations were not shown in TD. The findings of this study indicate that, in order to prevent growth related reductions in extensibility in children with SCP, clinical interventions treating hyper ankle dorsiflexion resistance should aim to increase both muscle physiological cross-sectional area and fascicle lengths, while preventing excessive longitudinal growth of tendinous structures.

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